REMARKS

The Present Invention and the Pending Claims

The present invention relates to a high-throughput method of distinguishing at least one molecule individually in a sample comprising multiple molecules. In the method of the invention, the molecule(s) to be detected are not amplified prior to being subjected to electrophoresis. In keeping with the inventive method, the molecule to be detected is imaged and its electrophoretic mobility is determined. Claims 1, 3-23, 57-65, and 67-91 are currently pending.

The Amendments to the Claims

Claims 1 and 65 have been amended to incorporate the subject matter of claims 2 and 66, respectively. Claims 2 and 66 have been cancelled. Claims 1, 21, 65, and 83 have been amended merely to replace the phrase "which method (or system) comprises" with "said method (or system) comprising" and the phrase "each detectably labeled molecule" with "the at least one detectably labeled molecule." Claims 1 and 65 also have been amended merely to replace the term "imaging" with "image." Accordingly, no new matter has been added by way of these amendments.

The Office Action

The Office Action made the following rejections:

(a) claims 1, 3-8, 11-13, 15-18, 21, 22, 58, 60-62, 65, 67-72, 74-76, 78-80, 83, 84, 86, 88, and 89 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over U.S. Patent 6,485,625 ("the Simpson '625 patent") in view of U.S. Patent 6,438,279 ("the Craighead '279 patent"),

(b) claims 2 and 66 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson '625 patent and the Craighead '279 patent in further view of U.S. Provisional Patent Application No. 60/180,810 ("the Fan '810 provisional application"),

(c) claims 9, 10, and 73 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson '625 patent and the Craighead '279 patent in further view of U.S. Patents 6,221,592 ("the Schwartz '592 patent") and 5,215,883 ("the Chu '883 patent"),

(d) claims 14, 23, 57, 77, and 85 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson '625 patent and

the Craighead '279 patent in further view of U.S. Patents 6,586,193 ("the Yguerabide '193 patent") and 6,120,667 ("the Hayashizaki '667 patent"),

(e) claims 19, 20, 63, 64, 81, 82, 90, and 91 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the Simpson '625 patent in view of the Craighead '279 patent,

(f) claims 59 and 87 are rejected under 35 U.S.C. § 103(a), as allegedly being unpatentable over the combined disclosures of the Simpson '625 patent and the Craighead '279 patent in further view of U.S. Patent 5,538,613 ("the Brumley '613 patent").

Reconsideration of these rejections is hereby requested.

Discussion of Rejections Under 35 U.S.C. § 103(a)

Claims 1, 3-8, 11-13, 15-21, 22, 58, 60-65, 67-72, 74-76, 78-83, 84, 86, and 88-91 stand rejected under Section 103 as allegedly being obvious over the Simpson '625 patent in view of the Craighead '279 patent. This rejection is traversed for the reasons set forth below.

Simpson discloses a method for the detection of molecules in a sample, wherein the molecules to be detected are amplified via polymerase chain reaction (PCR) prior to electrophoresis and spectroscopic analysis (see Simpson '625 patent at, e.g., col. 6, lines 35-42, and col. 29, line 24, through col. 30, line 30). Thus, Simpson describes the detection of many molecules of a single type. Craighead discloses a method for detecting single fluorophore-labeled molecules (e.g., DNA) in a sample by electrophoresing the molecules in the sample through an integrated flow channel/optical waveguide device (see Craighead '279 patent at, e.g., col. 5, lines 48-57, and col. 7, lines 59-67). Craighead further discloses measuring the velocity of each molecule moving through the flow channel one at a time (see Craighead '279 patent at, e.g., col. 7, lines 63-67, col. 17, lines 43-48, and claim 8).

In distinct contrast, claim 1, as amended, is directed to a *high-throughput* method of distinguishing at least one molecule individually in a sample comprising multiple molecules, said method comprising: (i) subjecting a sample comprising multiple molecules, at least one molecule of which is detectably labeled, to electrophoresis, wherein the multiple molecules are not amplified prior to being subjected to electrophoresis, (ii) imaging the electrophoretic mobility of the at least one detectably labeled molecule over time by detecting the position of the detectable label of the at least one detectably labeled molecule over time and, optionally, at the same time, dispersing the image by a transmission grating for spectroscopic analysis, and (iii) determining the electrophoretic mobility of the at least one detectably labeled molecule and, optionally, determining the molecular spectrum of the at least one detectably

labeled molecule, thereby distinguishing at least one molecule individually in a sample comprising multiple molecules.

Claim 65, as amended, is directed to a *high-throughput* method of distinguishing at least one molecule individually in a sample comprising multiple molecules, said method comprising: (i) introducing a sample comprising multiple molecules in free solution, at least one molecule of which is detectably labeled, into a sample channel, wherein the multiple molecules are not amplified prior to being introduced into the channel, (ii) simultaneously imaging the position of the at least one detectably labeled molecule by detecting the position of the detectable label of the at least one detectably labeled molecule and dispersing the image by a transmission grating for spectroscopic analysis, and (iii) determining the molecular spectrum of the at least one detectably labeled molecule, thereby distinguishing *at least one* molecule individually in a sample comprising multiple molecules.

The method defined by the pending claims is "high-throughput" in that it allows the simultaneous analysis of multiple molecules in a given sample (see specification of subject application at, for example, page 11, lines 24-25). Neither Simpson nor Craighead discloses or remotely suggests a *high-throughput* method that can distinguish *at least one* molecule individually in a sample comprising multiple molecules, wherein the molecules are not amplified prior to being subjected to electrophoresis, as required by the pending claims. In contrast, Simpson discloses measuring the mobility of *multiple* copies of the same DNA molecule, while Craighead discloses measuring the mobility of a single molecule one at a time as each molecule migrates through the electrophoretic channel. As such, Simpson and Craighead do not disclose every element of claim 1 or claim 65, alone or in combination. Accordingly, the invention defined by claims 1, 3-8, 11-13, 15-21, 22, 58, 60-65, 67-72, 74-76, 78-83, 84, 86, and 88-91 is unobvious in view of the Simpson '625 and Craighead '279 patents.

Applicants further submit that claims 1, 3-8, 11-13, 15-21, 22, 58, 60-65, 67-72, 74-76, 78-83, 84, 86, and 88-91 are patentable over Simpson and/or Craighead in view of the Fan '810 provisional application. Assuming the Fan '810 provisional application is prior art, it is relied upon solely for its purported teaching of methods for gene expression profiling that do not require target-specific amplification. In contrast to the claimed invention, the method disclosed in the Fan '810 provisional application requires PCR amplification of oligonucleotide primer sequences hybridized to cellular RNA prior to expression analysis (see, e.g., page 4, "Part I"). Accordingly, the Fan '810 provisional application does not satisfy the deficiencies of the other cited references as discussed above.

The Schwartz '592 patent and the Chu '883 patent are relied upon solely for their purported teachings of photobleaching during nucleic acid sequencing and during electrophoresis, respectively. Accordingly, neither the Schwartz '592 patent nor the Chu '883 patent satisfies the deficiencies of the other cited references as discussed above. Therefore, claims 9, 10, and 73 are patentable.

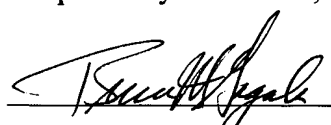
The Yguerabide '193 patent is relied upon solely for its purported teaching of the use of equilateral prisms to enhance the signal to noise ratio in analyte assays, while the Hayashizaki '667 patent is relied upon solely for its purported teaching of the use of a pinhole in an electrophoresis apparatus. The Brumley '613 patent is relied upon in the Office Action solely for its purported teaching of the use of a microscopic objective lens in an electrophoresis analyzer. Accordingly, neither the Yguerabide '193 patent, the Hayashizaki '667 patent, nor the Brumley '613 patent satisfies the deficiencies of the other cited references as discussed above. Therefore, claims 14, 23, 57, 59, 77, 85, and 87 are patentable.

In view of the foregoing, all of the pending claims are patentable over the cited references. Applicants request that the rejections be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,



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